and multiparticulate forms. New claim 54 recites two specific rate-controlling polymers, which are identified in the specification at page 15, lines 17 and 21.

II. SUMMARY OF THE INVENTION

The claimed invention relates to the surprising discovery of solid dose controlled release nanoparticulate active agent compositions. The controlled release compositions provide for the therapeutically effective release of an incorporated nanoparticulate active agent in a patient for a time period ranging from about 2 to about 24 hours. This discovery was surprising because nanoparticulate active agent compositions are designed for immediate, fast release. Such fast release results from the nanoparticulate size of the active agent, having a large surface area in relation to the volume, which results in rapid dissolution of the active agent following administration. However, rapid dissolution is contrary to the goal of controlled release formulations.

Applicants unexpectedly discovered that nanoparticulate active agent compositions could effectively be formulated into controlled release formulations. This is not shown or suggested by the cited prior art.

III. CLAIMS 2 AND 31 ARE DEFINITE

Claims 2 and 31 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner maintains that recitation of broad and narrow ranges within the same claims renders the claims ambiguous because it is not clear whether the narrow ranges are required features. Applicants traverse this ground for rejection.

Applicants respectfully submit that claims 2 and 31 are definite as written. The claims are in proper Markush form, with particle sizes in each range being alternative embodiments. That is, the average particle size of the nanoparticulate drug may be: (a) less than about 800 nm, (b) less than about 600 nm, (c) less than about 400 nm, (d) less than about 300 nm, (e) less than about 250 nm, (f) less than about 100 nm, or (g) less than about 50 nm.

The Examiner's concern appears to stem from the fact that some particle sizes fall within multiple ranges. For example, a particle size of 249 nm falls within groups (e), (f), and (g). Nonetheless, it is clear that a particle size of 249 nm comes within the scope of the claims. Therefore, the fact that a particle size may fall within several size ranges does not render the claims indefinite. See MPEP § 2173.05(h) (stating: "The mere fact that a

compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, 'selected from the group consisting of amino, halogen, nitro, chloro, and alkyl' should be acceptable even though 'halogen' is generic to 'chloro.'").

Because claims 1 and 31 are definite, in accord with 35 U.S.C. § 112, second paragraph, Applicants respectfully request withdrawal of the rejection.

IV. THE CLAIMS ARE PATENTABLE OVER LIVERSIDGE ET AL.

Claims 1-22 and 25-35 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,145,684 ("Liversidge et al."). Applicants respectfully traverse this ground of rejection.

A. Summary of Liversidge et al.

The claimed invention constitutes an improvement over commonly-owned Liversidge et al. *See* page 5, lines 25-27, of the application. Liversidge et al. teach nanoparticulate compositions comprising active agents and surface stabilizers, but do not teach incorporation of such nanoparticulate compositions into controlled release dosage forms.

B. The Examiner's Basis for the Rejection of the Claims over Liversidge et al.

In support of the rejection, the Examiner stated that Liversidge et al. disclose nanoparticles made of a drug substance and a surface stabilizer adsorbed to the surface thereof, excipients for making pharmaceutical compositions, and solid dose forms of such compositions. The Examiner further asserted that Liversidge et al's. "teaching of cellulose polymers in the composition reads on applicant's claim to both a surface stabilizer and a rate controlling polymer, because [the specification] states that a suitable surface stabilizer includes various polymers, therefore the cellulose polymers can perform both desired functions." The Examiner then "strongly urge[d]" Applicants to provide comparative data to prove that the compositions of Liversidge et al. behave differently than the claimed compositions. Applicants respectfully disagree with the Examiner's conclusion.

C. Controlled Release Nanoparticulate Compositions Behave Differently than the Compositions of Liversidge et al.

As requested, Applicants submit herewith comparative data demonstrating a stark difference between the rapid release of nanoparticulate drug compositions taught by Liversidge et al., and Applicants' claimed controlled-release nanoparticulate active agent compositions. The data is presented by Dr. Rajeev Jain in the attached declaration under 37 C.F.R. § 1.132 ("Jain Declaration").

Dr. Jain describes two examples in his declaration. In the first, an immediate release formulation (per Liversidge et al.) and a delayed release formulation (per the present invention) of the drug Compound A were prepared. The composition of the two formulations was identical, except that the delayed release formulation additionally contained a coating of polyvinyl acetate phthalate as a controlled release polymer.

As taught in the Jain Declaration, in an acid environment like that of the stomach, the immediate release formulation rapidly dissolved, which means the drug would immediately become available upon ingestion by a patient. *See* ¶ 13 of the Jain Declaration. By contrast, the delayed release formulation survived, essentially intact, for two hours in a highly acidic environment. *See* ¶ 14 of the Jain Declaration. The delayed release formulation dissolved rapidly in a pH environment approximating that of the small intestine, however. *See* ¶ 14 of the Jain Declaration. Thus, drug in the delayed release formulation would not become available until passing through a patient's stomach and into the small intestine.

In the second example, an immediate release formulation (per Liversidge et al.) and an extended release formulation (per the present invention) of the drug Compound B were prepared. The extended release formulation incorporated the nanoparticulate drug composition into a controlled release matrix with hydroxypropyl methyl cellulose and hydroxypropyl cellulose. In *in vitro* simulations, the immediate release formulation completely dissolved within 30 minutes. *See* ¶ 17 of the Jain Declaration. By contrast, the extended release formulation slowly dissolved over the course of 20 hours. *See* ¶ 20 of the Jain Declaration.

These examples underscore the very different effects that result from administering the compositions taught by Liversidge et al. relative to those presently claimed. Liversidge et al. teach compositions useful for rapid and immediate drug delivery. By contrast, the claimed

compositions deliver active agents in a controlled manner, including extended release and delayed release. Because the rate of an active agent's dissolution generally directly correlates with its surface area, the development of controlled-release nanoparticulate active agent formulations, as claimed, was surprisingly unexpected.

D. Controlled Release Nanoparticulate Compositions have Different Structures than the Compositions of Liversidge et al.

The Examiner noted that certain surface stabilizers, such as cellulose polymers, may also function as rate-controlling polymers (pg. 3, 2nd full ¶ of the Office Action), and therefore concluded that it would have been obvious to make controlled release nanoparticulate compositions using an agent that functions both as a surface stabilizer and as a rate-controlling polymer. Applicants respectfully disagree.

For a controlled release formulation to have a desired active agent release profile, rate-controlling polymers must be properly designed into the formulation's structure. That is, a polymer that is merely associated with the surface of an active agent to maintain a particle size (*i.e.*, functioning as a surface stabilizer) will not have a rate-controlling effect. Exemplary formulations in which polymers exert a rate-controlling effect are detailed at page 5, line 28, through page 7, line 15, of the specification.

As Chang et al. taught, "[d]esign of a sustained-release product is normally a very difficult task . . ." Chang et al., "Sustained Drug Release from Tablets and Particles through Coating," Lieberman et al., eds., *Pharmaceutical Dosage Forms: Tablets*, Vol. 3, p. 201 (Marcel Dekker, Inc., New York) (already of record). This is because:

> [s]uccessful fabrication of sustained-release products . . . involves consideration of the physical-chemical properties of the drug, pharmaco-kinetic behavior of the drug, route of administration, disease state to be treated and, most importantly, placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug.

Id. at 199.

Due to the inherent difficulties of designing controlled-release active agent products and the fact that nanoparticulate active agents generally act very quickly due to their large surface area, one skilled in the pharmaceutical arts at the time the claimed invention was made would not have been motivated to make the claimed compositions, and would not have

had a likelihood of success in doing so. Accordingly, the claimed compositions were not obvious, and Applicants respectfully request withdrawal of the rejection.

V. CONCLUSION

Applicants courteously request reconsideration of this application in view of the above amendments and remarks. This application is now in condition for allowance, and early notice to that effect is respectfully solicited.

If any fees are due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: Jan 15, 2003

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MARKED-UP VERSION OF THE CLAIMS

1. (Twice Amended) A controlled release nanoparticulate composition comprising:

(a) a **nanoparticulate drug composition comprising a** poorly soluble nanoparticulate drug to be administered **and at least one surface stabilizer associated with the surface of the nanoparticulate drug, wherein the nanoparticulate drug has [having]** an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have an average particle size of less than about 1000 nm when measured by light scattering techniques**, and**

(b) **[at least one surface stabilizer associated with the surface of the nanoparticulate drug, and**

(c)] at least one pharmaceutically acceptable rate-controlling polymer, wherein**: (i) the rate-controlling polymer is integrated in a rate-controlling matrix with the nanoparticulate drug composition or coats the nanoparticulate drug composition, and (ii)** the **controlled release nanoparticulate** composition provides controlled release of the nanoparticulate drug for a time period ranging from about 2 to about 24 hours.

2. (Twice Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the effective average particle size of the nanoparticulate drug is selected from the group consisting of less than about 800 nm, less than about 600 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm, wherein at least 50% of the drug particles have an average particle size of less than about 800, 600, 400, 300, 250, 100, or 50 nm, respectively, when measured by light scattering techniques.

3. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the concentration of the polymer is from about 5 to about 95% (w/w).

4. (Amended) The **controlled release nanoparticulate** composition of claim 3, wherein the concentration of the polymer is from about 10 to about 65% (w/w).

5. (Amended) The **controlled release nanoparticulate** composition of claim 1 additionally comprising a binder agent in an amount of from about 0.1 to about 10% (w/w).

6. (Amended) The **controlled release nanoparticulate** composition of claim 1 additionally comprising a lubricant in an amount of from about 0.1 to about 10% (w/w).

7. (Amended) The **controlled release nanoparticulate** composition of claim 6, wherein the lubricant is selected from the group consisting of magnesium stearate, hydrogenated vegetable oil, and stearic acid.

8. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the solid dose formulation is made by wet granulation.

9. (Twice Amended) The **controlled release nanoparticulate** composition of claim 1 formed by wet granulation, wherein water is added to the nanoparticulate drug, surface stabilizer, and polymer to form granules prior to forming the solid dose of the controlled release formulation.

10. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the rate-controlling polymer is selected from the group consisting of gum arabic, agar, guar gum, cereal gums, dextran, casein, gelatin, pectin, carrageenan, waxes, shellac, hydrogenated vegetable oils, polyvinylpyrrolidone, hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcelluose (HPMC), sodium carboxymethylcellulose (CMC), poly(ethylene) oxide, alkyl cellulose, ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydrophilic cellulose derivatives, polyethylene glycol, polyvinylpyrrolidone, cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl acetaldiethylamino acetate, poly(alkylmethacrylate), poly(vinyl acetate), polymers derived from acrylic or methacrylic acid and their respective esters, and copolymers derived from acrylic or methacrylic acid and their respective esters.

11. (Amended) The **controlled release nanoparticulate** composition of claim 10, wherein the rate-controlling polymer is **hydroxypropylmethyl cellulose (**HPMC**)**.

12. (Amended) The **controlled release nanoparticulate** composition of claim 10, wherein the rate-controlling polymer is a polymer derived from acrylic or methacrylic acid and their respective esters or copolymers derived from acrylic or methacrylic acid and their respective esters.

13. (Twice Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the poorly water soluble nanoparticulate drug is present in an amount of from about 1 μg to about 800 mg.

37. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the surface stabilizer is selected from the group consisting of gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, Tetronic 1508®, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), Crodestas SL-40®, SA9OHCO, decanoyl-N-methylglucamide, n-decyl -D-glucopyranoside, n-decyl -D-maltopyranoside, n-dodecyl -D-glucopyranoside, n-dodecyl -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl--D-glucopyranoside, n-heptyl -D-thioglucoside, n-hexyl -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl--D-glucopyranoside, and octyl -D-thioglucopyranoside.

38. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the drug is selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antiasthma agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antitussives, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, antipyretics, immunosuppressants, immunostimulants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, bronchodilators, cardiac inotropic agents, chemotherapeutics, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, proteins, polypeptides, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, hormones, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vaccines, vasodilators, and xanthines.

39. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the drug is selected from the group consisting of alprazolam, amiodarone, amlodipine, astemizole, atenolol, azathioprine, azelatine, beclomethasone, budesonide, buprenorphine, butalbital, carbamazepine, carbidopa, cefotaxime, cephalexin, cholestyramine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clonazepam, clozapine, cyclosporin, diazepam, diclofenac sodium, digoxin, dipyridamole, divalproex, dobutamine, doxazosin, enalapril, estradiol, etodolac, etoposide, famotidine, felodipine, fentanyl citrate, fexofenadine, finasteride, fluconazole, flunisolide, flurbiprofen, fluvoxamine, furosemide, glipizide, gliburide, ibuprofen, isosorbide dinitrate, isotretinoin, isradipine, itraconazole, ketoconazole, ketoprofen, lamotrigine, lansoprazole, loperamide, loratadine, lorazepam, lovastatin, medroxyprogesterone, mefenamic acid, methylprednisolone, midazolam, mometasone, nabumetone, naproxen, nicergoline, nifedipine, norfloxacin, omeprazole, paclitaxel, phenytoin, piroxicam, quinapril, ramipril, risperidone, sertraline, simvastatin, terbinafine, terfenadine, triamcinolone, valproic acid, zolpidem, and pharmaceutically acceptable salts thereof.

40. (Amended) The **controlled release nanoparticulate** composition of claim 1, wherein the drug is selected from the group consisting of naproxen, glipizide, and nifedipine.